Insect Sting Anaphylaxis

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• **Anaphylaxis from insect stings, which is considerably commoner than has been recognized, is a distinct emergency, requiring prompt and energetic treatment.**

Such reactions require the immediate intramuscular or deep hypodermic injection of 0.5 cc of 1:1000 epinephrine, which may have to be repeated shortly. After the initial critical phase is passed, there may be indication for intramuscular antihistamines and corticosteroids.

Persons who have survived insect sting anaphylaxis should be immunized with insect antigens for a minimum period of three years and perhaps indefinitely. The choice between pure venom and extracts of whole insect bodies rests with the physician, although the latter are far more often used.

Until immunization has become effective susceptible persons must carry with them at all times a kit containing epinephrine for both injection and aerosol use, and they must be trained by physicians in the proper use of these preparations.

ANAPHYLACTIC REACTIONS to the stings of insects, fulminant by nature and responsible for a disturbing number of fatalities annually, have been the subject of numerous reports. There is excellent reason to believe that such phenomena are considerably more common than is generally recognized. In addition to the sizable number of properly diagnosed but unreported reactions seen each year, there is likelihood that many deaths from insect sting are incorrectly ascribed to heat prostration, myocardial infarction or causes unknown.

Parrish[12] has appropriately called stinging insects "giant killers," since these tiny arthropods are more deadly than poisonous snakes. Data from the National Center for Health Statistics, U.S. Public Health Service, show that during the ten-year period 1950 through 1959, 50 per cent of all deaths from venomous animals in the United States were caused by the stings of insects. Poisonous snakes accounted for 138 deaths, while stinging insects caused 299 during the same period. Bees killed 124 persons, wasps 69, yellow jackets 22, hornets 10, and ants 4.

Insect sting anaphylaxis, like its counterpart resulting from injections of penicillin and horse serum (as in tetanus antitoxin), constitutes a true emergency, in which time and proper treatment are indeed of the essence. General physicians, internists, pediatricians and industrial physicians particularly should become aware of this problem, and all physicians would be well advised to formulate a plan for the immediate treatment of such cases.

The earliest record of death from insect sting is contained in the hieroglyphics found at the tomb of King Menes of Egypt,[4] who probably was stung to death by a wasp or hornet in 2641 B.C. In 1765, Desbrest described a fatality from a bee sting above the eyebrow. Delaistre in 1776 reported a death from a hornet sting in the palate. The first report in the American literature likely was by Mease, who in 1811 described a man who was stung in the nasal septum by a bee and died 30 minutes later.

Insects are responsible for less severe clinical manifestations of hypersensitivity as well, the more prominent examples being asthma, allergic rhinitis, generalized urticaria and papular urticaria. The allergen in such cases enters by inhalation of scales and dust from the living or dead insects or by instillation of material through the mouth parts of the biting insects. More than 30 different insects have been identified in such allergic reactions, including the aphid, beetle, butterfly, caddis fly, citrus fruit fly, cricket, deer fly, flea, gnat, house fly, locust, louse, Mexican kissing bedbug, midge, moth, mushroom fly, May fly, sewage filter fly, weevil and punky. The punkies, or black gnats, were called "no-see-ums" by the Indians, who found them to be both pestiferous and elusive.

The Phylum Arthropoda, which includes more species than all of the other phyla of the animal kingdom together, comprises such classes as the Crustacea (lobster, crab, water flea), Diplopoda (millipede), Chilopoda (centipede), Arachnida (spider, scorpion), and the Insecta (Hexapoda) or true insects. The stinging insects belong to the order Hymenoptera, which is the largest and most specialized order of insects, comprising more than 14,000 species in North America. The majority of stings are by the social (as distinguished from the solitary) species. The principal offenders (Figure 1) are the honeybee (Apis mellifera), paper wasp (Polistes aurifer), yellow jacket (Vespula diabolica), and hornet (Dolichovespula maculata). Also capable of stinging but responsible for a minority

Submitted June 13, 1963.

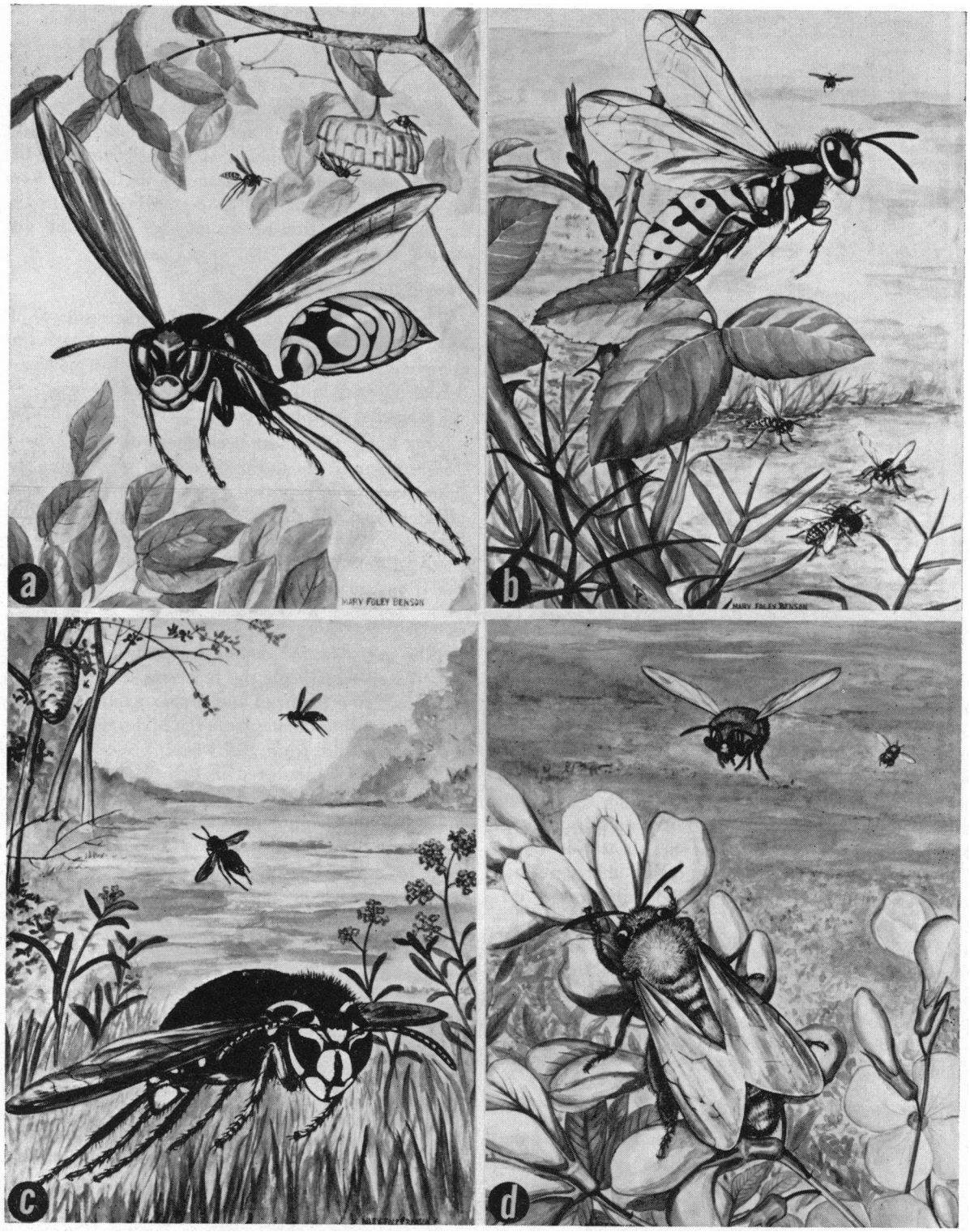

Figure 1.—*a.* Paper wasp (Polistes aurifer); *b.* Yellow jacket (Vespula diabolica); *c.* Black hornet (Dolichovespula maculata); *d.* Honeybee (Apis mellifera). From Hollister-Stier Laboratories, Spokane, Wash.

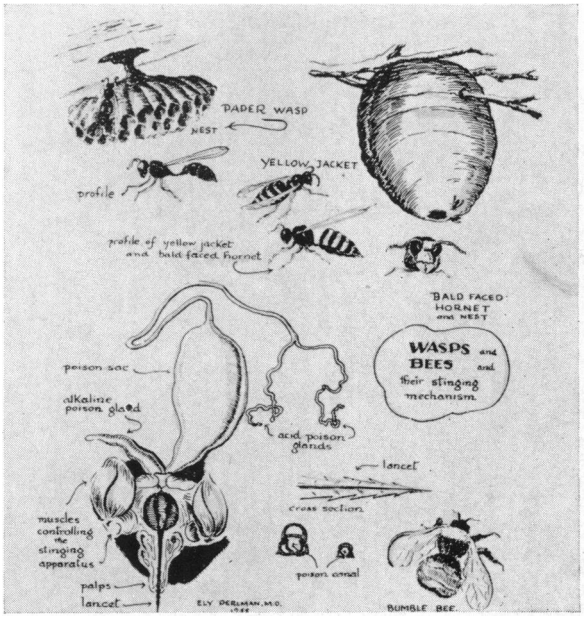

Figure 2.—Wasps and bees and their stinging mechanisms. From Perlman, E., J. Mt. Sinai Hosp., N. Y., 22:336, 1955.

of severe reactions are the bumblebee (Bombus) and several species of ants (Formicidae).

The honeybee and the bumblebee are members of the family Apidae. The paper wasp, hornet, and yellow jacket belong to the Vespidae or wasp family, and therefore are closely related. The paper wasp is readily identified by its spindle-shaped abdomen, which tapers at both ends. An untrained person would find great difficulty differentiating the hornet and yellow jacket, since the body contour is very similar and the colors in some species are identical. The honeybees are attracted to clover and therefore are found frequently in lawns. Yellow jackets build nests in the ground, under rocks and in walls of old buildings. The hornet builds large, oval, *papier-maché*-like nests usually in trees, while the paper wasps' open combs are in sheltered places such as garages, porches and under eaves. Bumblebees make small nests underground with relatively few inhabitants.

Sting Mechanism

The sting mechanism—the shaft that pierces the victim's skin—consists of a modified ovipositor and hence is found only in the female insect. The workers (abortive females) and the queen are the only honeybees with a sting, and the workers are unique in being the only insects to die after stinging. The worker bee leaves the sting with attached poison sac in the victim's flesh and then dies from self-inflicted evisceration.[2] The queen bee uses her sting only to exterminate rival queens. Hornets, yellow jackets, paper wasps, bumblebees and ants can sting repeatedly.

The sting mechanism of the honeybee (Figure 2) consists of a barbed shaft containing two hollow lancets or darts.[1] Attached to this apparatus are two poison glands, one acid and one alkaline. Prominent barbs on the shaft anchor the sting firmly in the human skin. The sting continues to inject venom even after it is detached from the bee, due to the rhythmic contraction of the muscles controlling the venom sac.

Toxic Effects of Venom

The toxic effects of venom are the result of its hemorrhagic, hemolytic, neurotoxic and histaminic components. The venom contains the most powerful dehydrogenase inhibitor known—even more powerful than that of cobra venom.

It is likely that most beekeepers develop considerable tolerance to the toxic effects of venom, and there have been reported cases of survival in spite of more than 400 stings within a period of minutes. However, the clinical manifestations of toxicity are vastly different than those of anaphylaxis. Either can occur without the other.

Insect Allergens

Ellis and Ahrens[3] demonstrated in 1932 that in hypersensitive patients the reactions to bee antigens prepared from the head and thorax exclusively were the same as those made from the abdomen and sting mechanism and from the whole bee. Benson and Semenov[1] who pioneered in this phase of study of allergic reactions, showed clearly that the sensitizing antigen is not confined to the venom. They found positive intradermal reactions in susceptible subjects to be equal one to another whether the antigen was prepared from the sting mechanism, from the whole body of the bee, or from pure venom. It was their opinion, and it is the prevalent one today, that sensitization is to an allergen inherent in the body of the insect, and that the sting causes sensitization only because the identical allergen of the bee's protoplasm is included in the venom.

Foubert and Stier[5] prepared separate alum-precipitated antigens from the pulped bodies of hornets, yellow jackets, wasps (Polistes) and honeybees. Freund adjuvant-antigen mixtures were then injected repeatedly into rabbits, following which the animals were bled, and the specimens of blood that had high precipitin titers were subjected to gel diffusion studies by the Ouchterlony technique. In addition, guinea pigs were sensitized with the alum-precipitated antigens by repeated injection and then challenged with intracardiac injections of the extracts. The gel diffusion studies showed that yellow jacket, hornet, wasp (Polistes) and honeybee con-

tain common antigens which probably are immunologically identical. In addition, each insect was found to contain several antigens specific for the individual genus. The anaphylactic shock experiments in guinea pigs identified yellow jacket as the most potent sensitizer. Black hornet was the least potent, and animals sensitized to bee antigen showed the least degree of heterologous sensitization.

Passive transfer and cross-test studies carried out by Loveless and Fackler[9] also led to the conclusion that yellow jacket, bald-faced hornet, paper wasp, honeybee and bumblebee possess a common allergenic specificity, while each has in its venom a component specific for that insect.

Clinical Features

The clinical manifestations of insect sting anaphylaxis are various combinations of the following: Weakness, restlessness, apprehension, dyspnea, urticaria, loss of consciousness, nausea, vomiting, generalized burning pain, profuse perspiration, severe abdominal cramps, frothing at the mouth, chills, vertigo, and evacuation of bowels and bladder. Symptoms usually begin within seconds or in some instances within two minutes of the sting and quickly reach a critical peak. When death occurs, it usually is within 30 minutes after the sting.

Necropsy Findings

The positive features at necropsy have included diffuse petechial hemorrhages in the viscera and other body tissues, pronounced visceral congestion, frothy or blood-tinged mucus in bronchi (Figure 3), laryngeal edema, pulmonary emphysema and edema and cerebral edema.

Mechanisms of Anaphylaxis

It has been suggested that anaphylaxis may be caused by the sting's puncturing of a vein in the dermis so that some of the venom enters the circulation immediately. While this may be remotely possible, the chances of its occurring are infinitesimal. In describing a patient who had been stung for years without reaction, and then had progressively increasing hypersensitivity to the stings within a period of a few months, Jex-Blake[7] said that "one cannot believe that the bees should have missed the veins a dozen times a year for 20 years and in the ensuing 9 months punctured them 11 times in succession."

As early as 1914, Waterhouse[15] concluded that severe reactions to insect sting "suggest a change which cannot be accounted for by the mere absorption of a minute quantity of irritant poison in a normal individual." Continuing, he said, "The depressed heart's action, the sudden urticaria and vasomotor phenomena, and the embarrassment of

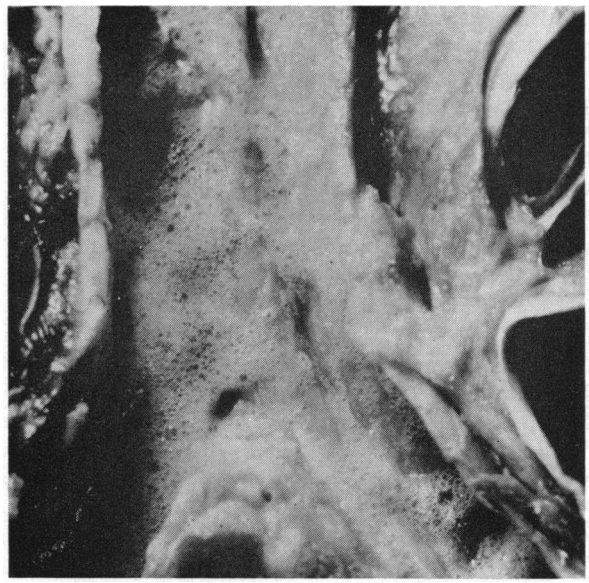

Figure 3.—Photograph of open trachea and main bronchi of patient who died of insect anaphylaxis. Note large quantity of mucus and frothy fluid in lumen. From Schenken, J. R., Amer. J. Clin. Path., 23:1216, 1953.

inspiration are all strongly suggestive of anaphylaxis . . ." We can better appreciate the remarkable astuteness of this observation when it is recalled that the term *anaphylaxis* had been introduced (by Portier and Richet) only twelve years previously!

The majority of reported cases of anaphylaxis in humans have been in persons who were exquisitely hypersensitive to horse serum, penicillin or insect stings. Anaphylaxis from rupture of an echinococcus cyst is comparatively rare, albeit the phenomenon occurred in a patient attended by the author when the cyst was ruptured during surgical removal. Injection of the anaphylactogenic protein is the route *par excellence* to produce the immunological explosion, and the sting mechanism of an insect is just as effective as a loaded syringe with needle. Davidson[2] has, in fact, referred to the barbed sting of a bee as "a living hypodermic."

There have been a number of instances reported of individuals becoming allergic both to the sting and to the inhalation of scales and debris shed by the same kind of insect. In such cases, the inhalation of insect debris caused asthma, while the sting induced anaphylaxis. An analogous situation, and one with which most physicians are more familiar, is the coexistence in the same person of asthma from inhalation of horse dander and anaphylactic sensitization to horse serum. Whether it be horse or insect protein, the "injection" can be fatal.

It may be that chances of anaphylaxis from two or more insect stings are greatly enhanced in many individuals who have become atopically sensitized to insect debris as an inhalant antigen. Since the

antigen protein in the two sources is so similar, anaphylactic antibodies may be developed more quickly and more abundantly after stings, as a result of previous exposure to the debris as an inhalant.

TREATMENT

Therapy for severe insect sting hypersensitivity should be considered from the standpoints of immediate, second stage, and long-term care.

1. *Immediate Treatment of Anaphylaxis*

The extreme rapidity of onset and the fulmination of symptoms demand prompt and energetic treatment. The specific and indeed the only drug for this emergency is aqueous epinephrine 1:1000; 0.3 cc to 0.5 cc should be given intramuscularly or by deep subcutaneous injection, and the site of injection massaged vigorously to hasten the absorption of the drug. The patient's response will dictate whether or not to repeat the dose. Failure to give epinephrine promptly for insect sting anaphylaxis is to invite fatality. There is no place in the early moments of treatment for such agents as antihistamines and corticosteroids.

2. *Second Stage Treatment*

a. If shock persists, in spite of epinephrine, it may be necessary to give a sympathomimetic agent such as metaraminol (Aramine® or Pressonex®), 100 mg in 500 cc isotonic saline solution intravenously.

b. A tourniquet should be placed above the sting site, if possible.

c. If the sting remains in the skin, it should be removed with a flicking or scraping motion of the fingernail or a knife blade.

d. Antihistamine may be given intramuscularly to combat the more prolonged effects of the allergic emergency. Chlorpheniramine maleate (Chlor-Trimeton,® 100 mg per cc), 0.5 to 1.0 cc; diphenhydramine (Benadryl,® 50 mg per cc), 0.5 to 1.0 cc; and tripelennamine (Pyribenzamine,® 25 mg per cc), 0.5 to 1.0 cc are useful.

e. Corticosteroids are useful in preventing such delayed reactions as urticaria. Dexamethasone (4 mg per cc), for example, is given intramuscularly in doses of 1.0 or 2.0 cc, repeated as necessary.

3. *Long-Term Care*

Every person who has survived insect sting anaphylaxis should have long-term desensitization (immunization) with appropriate insect antigens. The Insect Allergy Committee[8] of the American Academy of Allergy has studied approximately 1,500 case histories of insect sting allergy, 311 concerning patients who were desensitized and restung. Eighty-eight per cent of the latter showed definite improvement, as evidenced by protection against subsequent stings. Although there should be no question about the propriety of such immunization, there is some disagreement about the type of therapeutic antigen and the method to use. Loveless[10] employs pure wasp venom from carefully excised venom sacs. In earlier work[9] she used an average of six sacsful of venom in six divided endermal doses over a period of two and one half hours. In later studies wasp venom was given in an Arlacel®-Atreol® emulsion (1:6.5 mixture). Loveless estimated that the single repository injection gives protection for a period of four to six months. Deliberate stings several weeks after treatment indicated good immunity in her patients, and the stings were used to further enhance and prolong the immunity.

Gaillard[6] gave 227 repository injections of mixtures containing pulped whole bodies of female yellow jackets, wasps, bees and hornets to 124 patients and found this treatment to be as effective as multiple aqueous injections. Two patients who received such treatment subsequently developed delayed positive skin reactions on retesting, the exact significance of which is not clear.

Loveless[14] cautioned against the indiscriminate use of therapeutic insect antigens. It was her contention that the administration of "extraneous proteins may set up over a long term such antibody responses as theoretically underlie periarteritis and similar disorders of obscure origin." She reasoned that the insect sting injects only venom, hence the sensitization must be to venom and not to whole insect body protein.

Atreol, a highly purified mineral oil, serves as an immunological adjuvant in the repository emulsions used by Loveless and Gaillard. Like all adjuvants, it is capable of enhancing antibody production significantly. It has been assumed generally that this process is as benign as it apparently is beneficial. A question[13] has been raised concerning the possible carcinogenic effects of mineral oil in the emulsion. While definite evidence of serious long-term ill-effects from repository injections in humans is lacking, the procedure probably will be the subject of critical scrutiny during the next few years.

Loveless encourages the identification of the offending insect by patient and physician, and feels that ideally the venom of that insect alone should be given. Mueller,[11] Foubert and Stier[5] and others have expressed belief that the patient seldom is able to identify the offending insect, and have taken the stand that an incorrect identification certainly is worse than none at all.

Immunization with extracts of whole bodies of insects is the method most commonly employed.

While there may be merit in the argument of Loveless against such therapy, there has been no evidence produced to show that the hundreds of thousands of injections of such antigens given by hundreds of allergists through the years has led to periarteritis nodosa or similar vascular lesions. Sensitive patients should be skin-tested with extracts of each of the principal insects, beginning with exceedingly weak concentrations. Mueller[11] recommended 1:100,000,000 as the initial concentration for this purpose. Decimal increases in concentration are applied at 15 to 20 minute intervals until positive reactions result. Fresh solutions for testing should be prepared every four weeks because of loss of potency. Negative reactions to skin tests, however, do not rule out allergic sensitivity to insects. A patient with a history of anaphylactoid symptoms following insect sting, but who has negative skin tests and cannot identify the insect, should be treated with an antigen composed of honeybee, hornet, paper wasp and yellow jacket. Walter and Coleman[14] found that 61 per cent of their patients had positive and 39 per cent had negative response to skin tests. Mueller[11] reported that 89 per cent of patients he studied were found to be allergic to more than one insect, and over 60 per cent showed sensitivity to three or four stinging insects.

Desensitization procedures carried out over a period of three years are considered by many to be adequate. While this is empirical, there has been some practical support for it. Walzer and Coleman[14] expressed belief that patients in whom stings produced only urticaria or angioedema may discontinue treatment at the end of three years, while those with more severe symptoms should be treated indefinitely.

A hypersensitive person who is being desensitized (immunized) to insect sting remains in jeopardy until such time as the desensitization becomes effective. It is not unusual for this to require several months of active treatment. During that interval, the patient must keep on or near his person at all times a kit (Figure 4) containing injectable epinephrine, epinephrine for nebulization, cotton sponges and alcohol. The following are particularly helpful:

1. Two ampins (Moore Kirk Laboratories, Inc.), each containing 0.5 cc of epinephrine USP, 1:000, sealed under pressure and connected ingeniously by rubber tubing to a sterile needle.

2. Medihaler-Epi® (Riker), a nebulizer which delivers an estimated 0.15 mg of epinephrine with each measured dose.

Pending development of adequate immunity from desensitization, the patient's life may depend on the self-administration of epinephrine within one or two

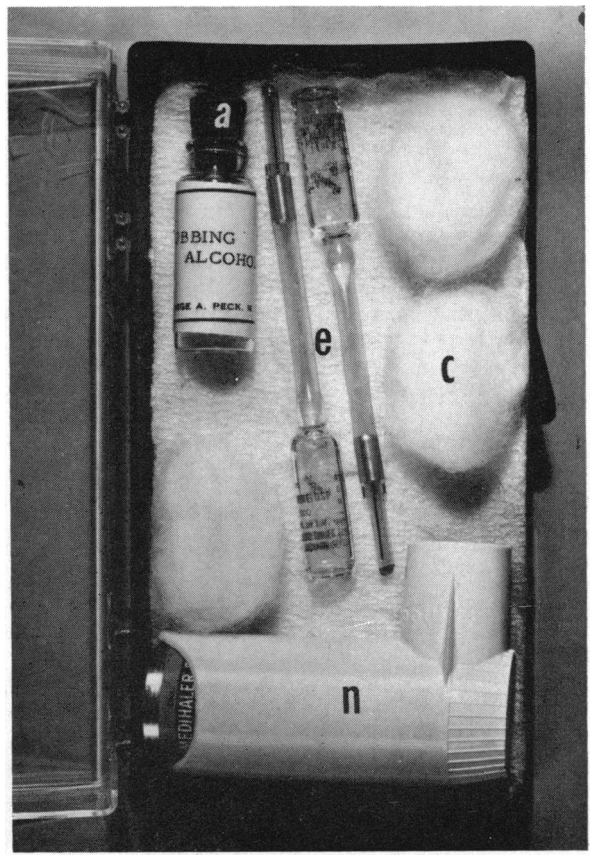

Figure 4.—Emergency insect sting kit. *a*, rubbing alcohol; *c*, cotton balls; *e*, epinephrine ampins; *n*, epinephrine nebulizer.

minutes after a sting. He should not use the drug indiscriminately, the indication for its use being the earliest appearance of any symptoms suggesting impending anaphylaxis. Once such symptoms have appeared, his fight is against time.

These are the instructions the patient is to follow:

1. Take two inhalations from the Medihaler-Epi® and hold breath in inspiration for five seconds or longer.

2. Give contents of 1 ampin of epinephrine into anterior thigh muscle, and vigorously massage injection site for 1 or 2 minutes.

3. Summon medical aid.

It has been proposed that sublingual isoproterenol be used instead of injectable epinephrine. While the former is unquestionably easier to administer, its speed of action and efficacy are distinctly less than the combined effects of the injected and inhaled epinephrine.

A person who is hypersensitive to insect stings should be warned against wearing perfumes, strong-scented hair preparations and vividly-colored clothing, which attract stinging insects. He also should avoid handling attractive flowers in their natural

habitat, as insects are much more likely to sting when there is apparent interference with the gathering of nectar.

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